Introduction

Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products

Anti-Infective Advisory Committee Meeting
October 26, 2009

Ed Cox, MD MPH
Office of Antimicrobial Products/ Office of New Drugs
Center for Drug Evaluation and Research

Outline

- Questions
- Microbiology subsection labeling
- Reasons for updating micro labeling
- Current status of micro labeling
- Processes to update
- “Breakpoints” guidance document
  - Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices – June 2009
- Characteristics and criteria FDA might consider in evaluating a standard and a standard development organization
- Approaches to updating the accumulated out-of-date microbiology labeling

Question #1

DISCUSSION QUESTION

Evaluation of a standard set by a nationally or internationally recognized standard development organization for possible recognition by FDA.

1. What characteristics or criteria should FDA consider when evaluating a standard (e.g., standards on susceptibility test interpretive criteria, quality control, and/or methods) and a nationally or internationally recognized standard development organization?

Question #2

DISCUSSION QUESTION

2. Given the considerable number of products in need of updating, and the fact that a number of these products may have been out-of-date for a number of years, it may be difficult to identify all of the information that supported the *Microbiology* subsection in labeling or the standards set in past years. How should we approach the updating of the accumulated out-of-date microbiology information in product labeling for systemic antibacterial drug products to facilitate updating in a timely manner?

Question #2 – cont'd

a. Given time and feasibility concerns, should the FDA evaluate each susceptibility test interpretive criterion, each set of quality control parameters, and the methods individually for each drug to see what information was used as the basis for the standard setting organization?

b. For updating the out-of-date microbiology labeling can we assume, in general, that the reference standard has more up-to-date information than the product labeling, unless we have specific information otherwise?

c. Other

Product Labeling

1 INDICATIONS AND USAGE
- 1.1 Indication #1
- 1.2 Indication #2

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- **12.4 Microbiology**

13 NON-CLINICAL TOXICOLOGY

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

Microbiology Subsection

- Mechanism of Action
- Mechanism of Resistance
- Interaction with Other Antimicrobials
- List of organisms with both in vitro and clinical data (“first list”)
- List of organisms with in vitro data (“second list”)
- Susceptibility Test Methods

Microbiology Subsection (cont'd)

- Susceptibility Test Methods
  - Dilution techniques
  - Diffusion techniques
  - Interpretive criteria usually in a table
  - Quality control parameters - table with acceptable quality control ranges
  - Includes references to standardized methods for susceptibility testing

Why Update Micro Labeling? - 1

Science

- Over time the relationship between susceptibility and response for a bacterial species and antibacterial drug may change
  - new mechanisms of resistance
- Quality control parameters may be refined to better assess the performance of the susceptibility test
- Microbiological testing methods may be refined to allow for more accurate and reliable performance of the test
  - e.g., modifications to the test medium or the inoculum
- Important to have current information to help guide appropriate selection of drugs to treat patients

Why Update Micro Labeling? - 2

Statute and Regulation

- Section 1111 of FDAAA requires FDA to "identify (where such information is reasonably available) and periodically update" susceptibility test interpretive criteria.
- Section 1111(c) requires FDA to make susceptibility test interpretive criteria publicly available "not later than 30 days after the date of identification and any update under . . . section [1111]."

- Application holders have a responsibility to update information in the labeling of their drug products (including antibacterial drug products) (see 21 CFR 201.56(a)(2)).

Updating micro labeling

- It has been difficult to keep microbiology labeling updated over time
- Sent letters asking applicant's to provide a plan for updating microbiology information in product labeling
  - Resulted in a number of questions
- Published Guidance
  - "Breakpoints" Guidance
  - Draft Technical Microbiology Guidance

[1] Guidance – Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices – June 2009

[2] Draft Guidance - Microbiological Data for Systemic Antibacterial Drug Products — Development, Analysis, and Presentation – September 2009

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Current Status of Microbiology Subsection Labeling

- Our evaluation of a sample of antibacterial drug labels found that a large proportion were in need of updating
  - interpretive criteria, quality control, and/or methods
- There are approx. 100 reference listed systemic antibacterial drugs for human use
- Total number of systemic antibacterial drug products for human use including all generics is approx. 600 to 700

Reference Listed Drug

- Reference Listed Drug (RLD)
  - the innovator product if still marketed
  - the designated generic, if innovator no longer marketed
- "Generics"
  - Update their labeling to conform to RLD
- For older antibacterial drugs a generic drug may be the RLD

Breakpoints Guidance - 1

Reminds Applicants of responsibility to periodically evaluate *Microbiology* Subsection

- Addressing the status of the *Microbiology* Subsection in their Annual Report
  - Application holders should also include in their annual report an assessment of whether the information in the *Microbiology* subsection of their product labeling is current or changes are needed (21 CFR 314.81(b)(2)(i) and 314.98(c)).
- Within 90 days of FDA publicly recognizing a standard relevant to their drug

Breakpoints Guidance - 2

- Once a standard has been recognized
- Describes procedures for updating *Microbiology* Subsection labeling (within 90 days)
  - Updating through reliance on a standard recognized by FDA

  or
  - Updating through submission of information that supports labeling different from a standard recognized by FDA
- If the Applicant believes no change is needed despite labeling that differs from the standard provide written justification to the FDA within 90 days following the publication of the *Federal Register* notice

Labeling Supplement to Change Microbiology Subsection Labeling

- Applicant can at any time submit a labeling supplement to update their labeling
  - submitting data that supports the proposed change in the information in the *Microbiology* Subsection of product labeling

Recognizing a Standard - 1

- The standard would need to be recognized by the Agency through publication in the *Federal Register*
- Agency scientifically evaluates each standard(s) and decides whether or not to recognize
- Agency can recognize the standard, in whole or in part

Recognizing a Standard - 2

- Recognition of a standard is only for the organisms that are in the Indications and Usage Section
- Cannot add organisms to the Indications and Usage Section through standard recognition
- Agency retains authority
- Agency identifies the recognized standard (title, date of the standard, and/or serial number) in the *Federal Register*

Recognizing a Standard - 3

- Seek the advice of the Anti-Infective Drugs AC on the characteristics and criteria that might be considered in selecting a standard
- Standards have been recognized in other parts of FDA
- To date we have not yet recognized a standard for antibacterial drug labeling

Possible Factors to Consider - 1

- Is the standard setting organization nationally or internationally recognized?
- Does the organization have procedures for addressing conflicts of interest?
- Does the organization have procedures for getting input from interested parties, including the public, on topics being discussed by the organization?
- Does the organization have procedures to provide timely information to the public as to when and where meetings will be held?
- Are the organization's meetings open to the public, and do they allow for public comment?
- Does the organization have established administrative procedures?

Possible Factors to Consider - 2

- Does the organization have established scientific standards?
- Are the standards developed by the organization applicable to the United States population?
- Is the information from the meeting, including minutes and scientific information discussed at the meeting, made publicly available?
- Are the standards developed by the organization available to persons who may want to review the standards?
- Does the organization publish its standard in a form that can be readily identified and referenced so that the standard could be clearly identified for the purposes of recognition?

Updating the Accumulated Out-of-date Microbiology Subsection of Antibacterial Drug Labeling

- There are a number of drugs approved a number of years ago in need of updating of *Microbiology* Subsection labeling
- It may be difficult to identify the information that supported the micro labeling years ago
- Similarly, for standards set over the last few decades, it may be difficult to identify the information that supported the standard
- It is our impression that over the years clinical microbiology laboratories have been relying upon reference standards when product labeling *Microbiology* Subsection is out-of-date

Options for Updating the Accumulated Out-of-Date Antibacterial Drug Labeling

a. Given time and feasibility concerns, should the FDA evaluate each susceptibility test interpretive criterion, each set of quality control parameters, and the methods individually for each drug to see what information was used as the basis for the standard setting organization?

b. For updating the out-of-date microbiology labeling can we assume, in general, that the reference standard has more up-to-date information than the product labeling, unless we have specific information otherwise?

c. Other

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REASONS FOR OUTDATED MICROBIOLOGY INFORMATION IN FDA LABELS

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- Reasons for outdated labels
  - Change in breakpoints due to:
    - Shift in susceptibility of wild type population
      - *Neisseria gonorrhoeae*
        - Penicillin
        - Spectinomycin
      - *Streptococcus pneumoniae*
        - Penicillin
      - Enterobacteriaceae
        - Carbapenems
      - *Staphylococcus aureus*
        - Semi-synthetic penicillins

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- Reasons for outdated labels (cont.)
  - New PK/PD information
    - Cephalosporins
    - Penicillin
  - New mechanisms of resistance
    - PBP2' (*mec*A gene)
    - New Beta lactamase classes
    - rRNA methylase (*erm*A gene)
    - TetM efflux protein (tetM gene)
    - Carbapenemases
    - Van type resistances (staph and enterococci)

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- Reasons for outdated labels (cont.)
  - Modified susceptibility test methods
  - New susceptibility test media
    - Haemophilus test medium
      - *Haemophilus* spp.
        - Ampicillin
        - Amoxicillin/clavulanate
        - Cefuroxime
        - Chloramphenicol
        - Ciprofloxacin
        - TMP/SMX
        - Tetracycline

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- Reasons for outdated labels (cont.)
  - Lysed horse blood medium
    - *Streptococcus pneumoniae*
      - Ampicillin
      - Cefaclor
      - Chloramphenicol
      - Tetracycline
    - Beta-hemolytic streptococci
      - Penicillin
      - Ampicillin
      - Vancomycin

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- Reasons for outdated labels (cont.)
- GC Agar base + supplement
  - *Neisseria gonorrhoeae*
    - Penicillin
    - Spectinomycin
    - Tetracycline
- Anaerobe medium
  - Variety of medium changes over the years

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- Reasons for outdated labels (cont.)
- Discrepancy between MIC and disc diffusion interpretive criteria
  - Extensive laboratory studies required to readjust relation between MIC and disc diffusion interpretive criteria
- Change in Quality Control Parameters
  - Requires input from clinical laboratories to recognize that changes are needed followed by extensive multi-laboratory studies to define change needed

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- Reasons for outdated labels (cont.)
- No FDA clinical microbiology laboratory capacity to address:
  - The effect of shift in antimicrobial susceptibility of wild type populations of microorganisms on interpretive criteria
  - Discrepancies between susceptibility test disk diffusion interpretive criteria and MIC interpretive criteria
  - Readjustment of susceptibility test quality control parameters
  - Needed changes in methods of susceptibility testing
  - PK/PD

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- Disconnect between FDA and clinical microbiology laboratory stakeholders
  - Limited FDA access to clinical laboratory personnel to obtain information on susceptibility testing

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FDA CLINICAL MICROBIOLOGY REVIEW OF ANTIMICROBIAL SUBMISSIONS

and

WHAT CLINICAL MICROBIOLOGY INFORMATION IS NEEDED TO UPDATE OUTDATED CLINICAL MICROBIOLGY INFORMATION IN FDA LABELS?

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- FDA REVIEW PROCESS
  - The FDA review process is conducted by experts in a variety of disciplines
    - Clinical microbiologists
    - Product quality microbiologists
    - Chemists
    - Toxicologists
    - Medical Officers
    - Pharmacologists
    - Bio-Pharmacologists
    - Statisticians
    - Regulatory Project Managers
    - Others as needed (e.g. immunologists, radiologists)

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- Information needed for setting interpretive criteria (breakpoints)
  - In vitro microbiological data
  - In vitro resistance markers (phenotypic and genotypic)
  - Animal and human PK/PD data
  - Clinical and microbiological outcome from prospective clinical trials
- No single set of information provides all necessary information

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FDA CLINICAL MICROBIOLOGY REVIEW OF ANTIMICROBIAL SUBMISSIONS

Pre-IND

- Information gathering process between Agency and Sponsor
- Preliminary discussions on:
  - Indications
  - Spectrum of antimicrobial activity
  - Mechanism of action of antimicrobial
  - Pharmacokinetics/Pharmacodynamics
  - Agency advice on approach to development
  - Design of Phase 1 studies (sponsor protocols reviewed)

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- Review of Submissions (cont.)
  - Phase 1 Clinical Microbiology Considerations
    - Characterization of:
      - in vitro susceptibility test conditions (e.g. pH, incubation environment)
      - correlation between different susceptibility test methods
      - mechanism(s) of action
        - bactericidal, bacteriostatic
      - mechanism(s) of resistance
        - incidence of resistance (e.g. spontaneous, hetero-resistance)
      - in vivo conditions that may affect activity of antimicrobial (e.g. body fluids)
    - pharmacokinetics/pharmacodynamics in animal models
  - In vitro susceptibility test QC parameters established

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- Review of Submissions (cont.)
  - Phase 1 (cont.)
    - Determination of in vitro activity against wild type population of microorganisms
      - Histograms of distributions for organism-antibacterial combinations constructed
        - Presents picture of whether only wild-type strains are present or whether isolates with elevated MICs are included

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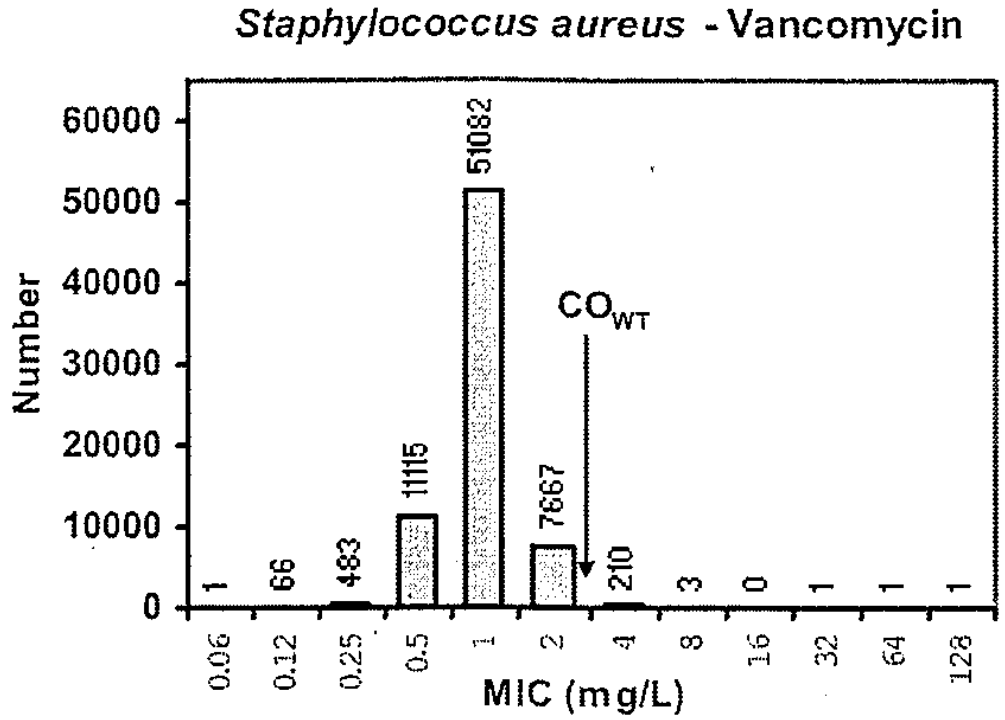

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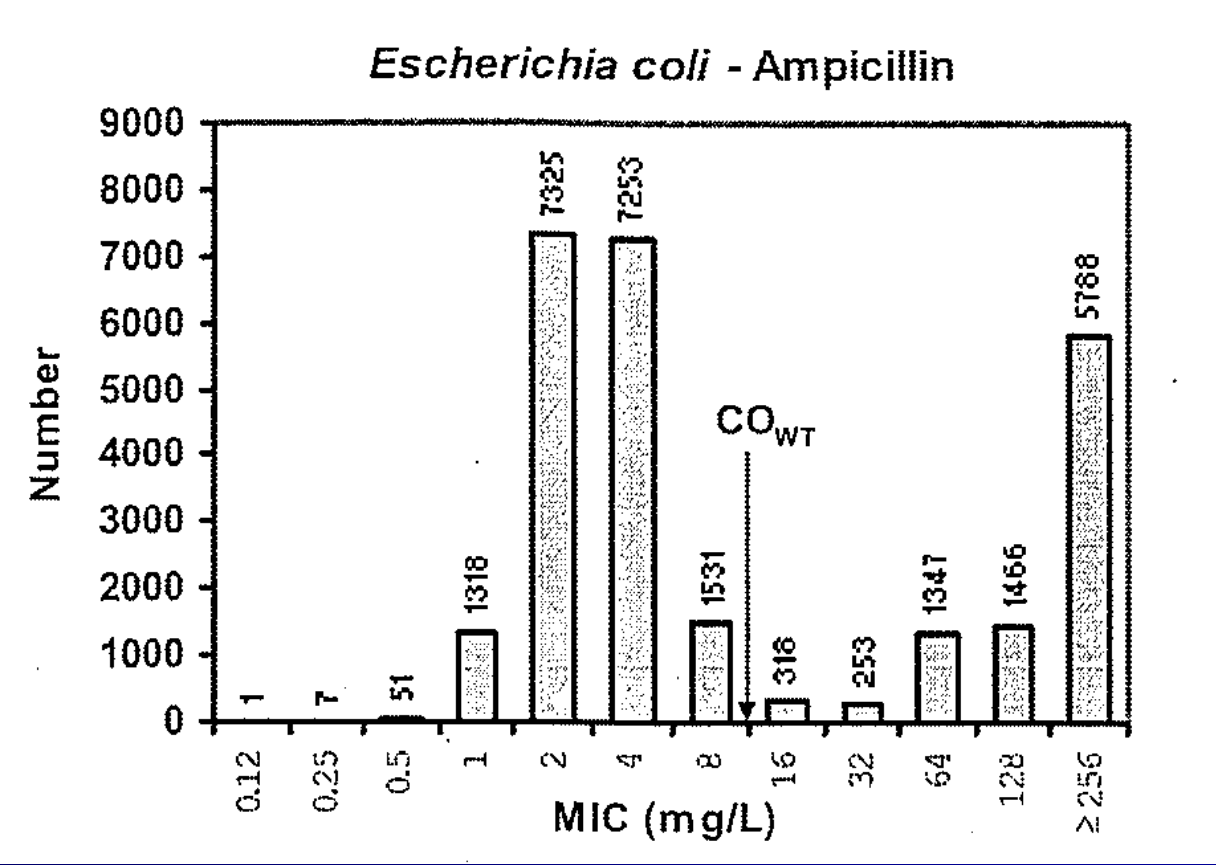

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- Review of Submissions (cont.)
  - Phase 1 (cont.)
- In vitro resistance markers
  - Phenotypic (e.g. beta-lactamase detection, screening plates, induction)
  - Genotypic (e.g. PCR for detection of mecA gene)

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- Review of Submissions (cont.)
  - Phase 1 (cont.)
- Determination of activity in appropriate animal model(s) of infection against specific pathogens
  - Screening model
    - Mouse protection model
  - Discrimative models
    - Lung infection, wound infection, etc. models

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- Review of Submissions (cont.)
  - Phase 1 (cont.)
- PK/PD studies in animals
  - Determine which relationship predicts efficacy of antimicrobial
    - Time above MIC (T>MIC)
    - Peak level to MIC ratio (C_{max}/MIC)
    - Ratio to area under curve over 24 hours (AUC_{24}/MIC)

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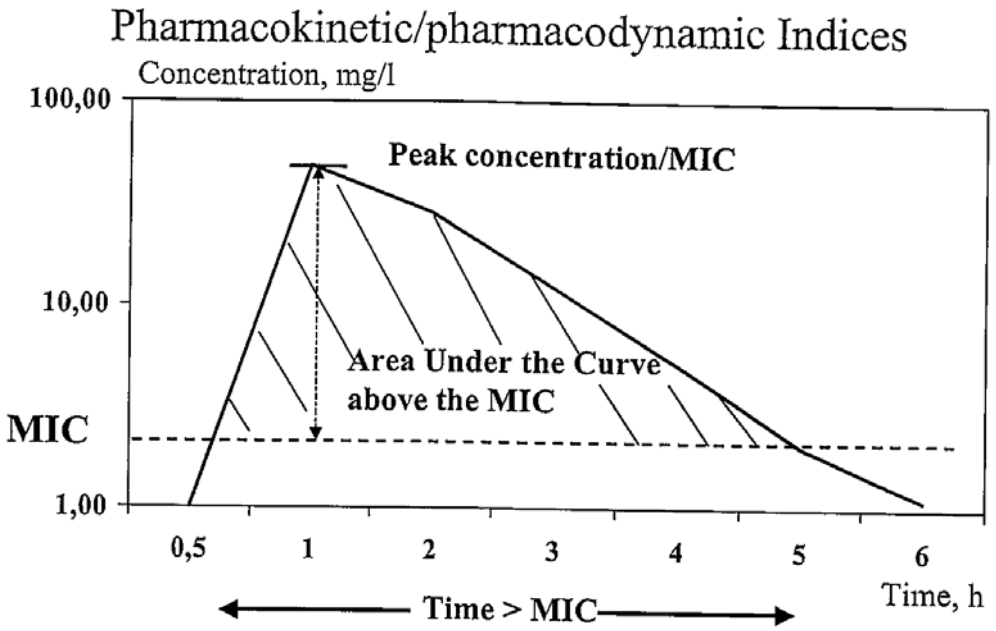

Fig. 1. PK parameters used for correlation with effect in vivo. The curve illustrates a random serum concentration curve of an antibiotic administered either orally or intramuscularly.

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- Review of Submissions (cont.)
  - Phase 1 (cont.)
- Post Antibiotic Effect (PAE)
  - Period of delayed regrowth, following drug removal
    - Immediate regrowth, moderate delay in regrowth, long delay in regrowth
      - Information is useful in determining dosage regimen
  - Determination of other characteristics of antimicrobial (e.g. ability to concentrate intracellularly)
  - Target Product Profile (TPP)
  - Design of Phase 2 studies (sponsor protocols reviewed)

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- Review of Submissions (cont.)
- Phase 2
- Determination of pharmacokinetics in normal and infected human subjects
- Limited efficacy testing in infected human subjects
  - clinical and microbiological evaluation of efficacy

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Table 3-30: Clinical and Microbiologic Response by MIC Value for Selected Baseline Isolates: Microbiologic Modified Intent-to-Treat Population in Studies 308 and 313 (Cont'd)

		---Tigecycline 50 mg---		---Levofloxacin---	
Pathogen	MIC (μg/ml)	Clinical Response Cure n / N	Microbiologic Response Eradication n / N	Clinical Response Cure n / N	Microbiological Response Eradication n / N
Streptococcus pneumoniae (Non-(PI,PR))	0.03	4/ 7	5/ 7	0/ 0	0/ 0
	0.06	40/ 43	41/ 43	0/ 0	0/ 0
	0.12	1/ 3	1/ 3	0/ 0	0/ 0
	0.5	0/ 0	0/ 0	4/ 5	4/ 5
	1	0/ 0	0/ 0	36/ 44	37/ 44
	2	0/ 0	0/ 0	2/ 2	2/ 2
	Total	45/ 53	47/ 53	42/ 51	43/ 51
Streptococcus pneumoniae (PISP)	0.06	4/ 5	4/ 5	0/ 0	0/ 0
	0.5	0/ 0	0/ 0	1/ 1	1/ 1
	1	0/ 0	0/ 0	5/ 5	5/ 5
	Total	4/ 5	4/ 5	6/ 6	6/ 6
Streptococcus pneumoniae (PRSP)	0.06	3/ 3	3/ 3	0/ 0	0/ 0
	0.12	0/ 1	1/ 1	0/ 0	0/ 0
	0.5	0/ 0	0/ 0	3/ 3	3/ 3
	1	0/ 0	0/ 0	1/ 2	2/ 2
	2	0/ 0	0/ 0	1/ 1	1/ 1
	Total	3/ 4	4/ 4	5/ 6	6/ 6

Abbreviations: MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; PI = penicillin intermediate; PR = penicillin resistant; PISP = penicillin intermediate *S. pneumoniae*; PRSP = penicillin resistant *S. pneumoniae*.
Source: MMMICC1 - 23JUN06 09:15

The clinical and microbiologic response by MIC value for all baseline isolates in the studies for the ME and m-mITT populations are summarized in 5.3.5.3, Efficacy Supportive Tables, CAP, ST 3-15 and ST 3-16, respectively.

The MIC values, clinical responses, and microbiologic responses of the selected baseline isolates excluding contaminants are summarized separately for those ME subjects with monomicrobial infections in Table 3-31 and those in polymicrobial infections in Table 3-32.

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- Review of Submissions (cont.)
- Phase 2
- Determine Estimated Target Attainment
  - used to establish preliminary MIC interpretive criteria

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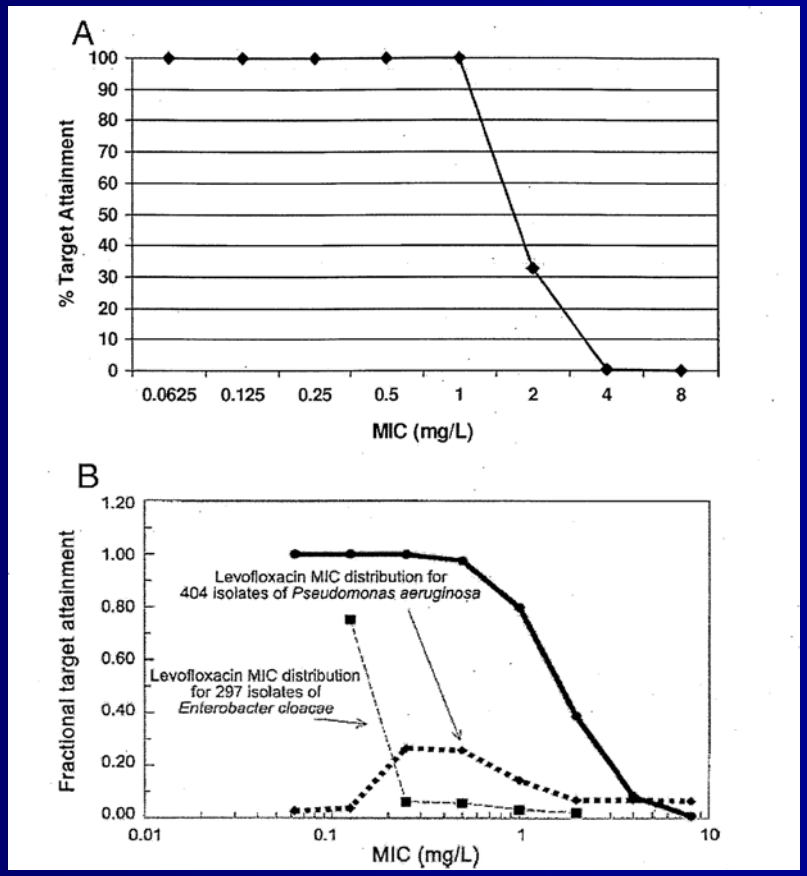

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- Review of Submissions (cont.)
- Phase 2
- Monte Carlo simulations (statistical technique where a population of values is simulated using the mean and standard deviation from a small PK/PD study to estimate breakpoint)

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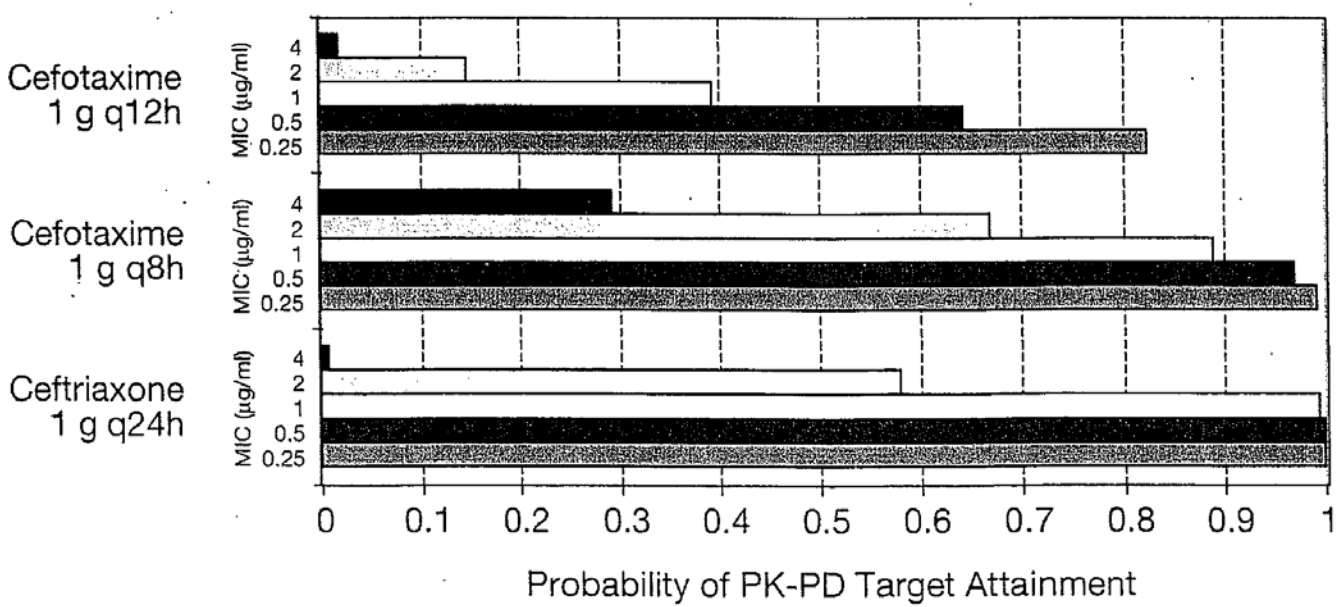

Figure 1. Fractional pharmacokinetic-pharmacodynamic (PK-PD) target attainment of ceftriaxone 1 g intravenously every 24 hours and cefotaxime 1 g intravenously every 8 and 12 hours against *Streptococcus pneumoniae*. These data were presented to Subcommittee on Antimicrobial Susceptibility Testing of the Clinical and Laboratory Standards Institute in January 2001 as decision support for susceptibility breakpoints for ceftriaxone and cefotaxime.[10] MIC = minimum inhibitory concentration.

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- Review of Submissions (cont.)
- Phase 2
- Provisional MIC breakpoint(s) for Phase 3 studies
  - Based on in vitro susceptibility data
  - PK/PD in animals and humans
  - Limited efficacy data from human clinical studies
  - Monte Carlo simulations

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- Review of Submissions (cont.)
- Phase 2
  - Preliminary microbiology subsection of package insert
  - Design of Phase 3 studies (sponsor protocols reviewed)
    - Adequate and well controlled studies

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- Phase 3 clinical trial **protocol** review
  - Microbiology considerations
    - Specimen and isolate identification and chain of custody
    - Specimen collection
    - Specimen transport
    - Specimen evaluation

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- Phase 3 clinical trial **protocol** review (cont.)
  - Specimen processing
  - Isolate identification methods
  - Isolate transportation
  - Isolate preservation
  - Susceptibility test methods

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- Phase 3 clinical trial **protocol** review (cont.)
- Microbiology considerations
  - Strain identification needs and method(s)
  - Foreign study microbial population similarity to United States microbial population
  - Determination of virulence factors

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- Review of **clinical trial results**
- Clinical microbiology considerations
  - Quality of specimens
  - Organism identifications
  - Susceptibility test QC results
  - Susceptibility test results

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- Review of **clinical trial results** (cont.)
  - Correlation of test results between local laboratory and reference laboratory
  - Correlation between provisional interpretive criteria and clinical isolate susceptibility results
  - MIC distribution of isolates seen in clinical trial versus MIC distribution seen from initial surveillance data

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Figure 4-69: Preclinical and clinical frequency distribution of tigecycline MICs (µg/ml) against *Streptococcus pneumoniae* (all isolates) (N=757, 184)

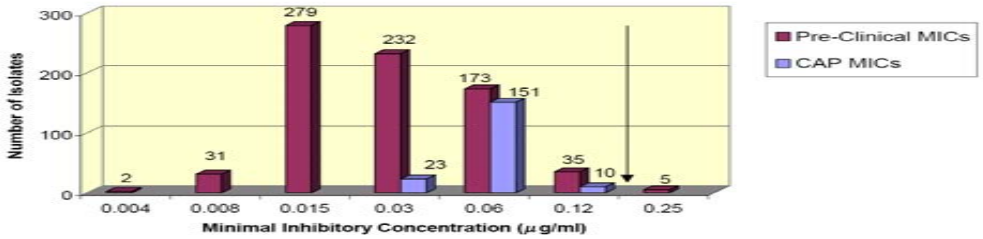
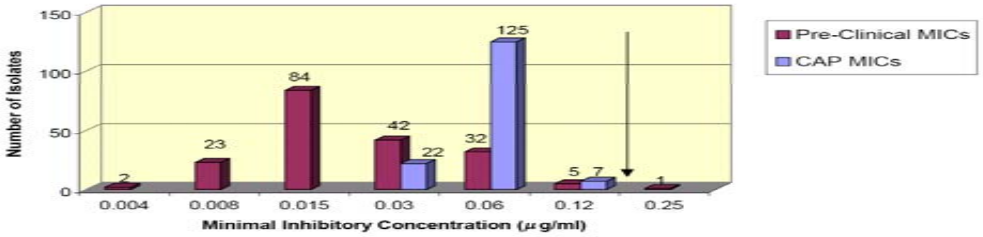


Figure 4-70: Preclinical and clinical frequency distribution of tigecycline MICs (µg/ml) against *Streptococcus pneumoniae* PSSP (all isolates) (N=189, 154)



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- Review of **clinical trial results** (cont.)
  - Correlation between MIC, clinical outcome, microbial eradication and virulence factors

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Table 3-29: Clinical and Microbiologic Response by MIC Value for Selected Baseline Isolates: Microbiologically Evaluable Population for Studies 308 and 313

Pathogen	MIC (µg/ml)	---Tigecycline 50 mg-- Clinical Response Cure n / N	Microbiologic Response Eradication n / N	---Levofloxacin-- Clinical Response Cure n / N	Microbiologic Response Eradication n / N
Haemophilus influenzae	0.12	2/ 2	2/ 2	13/ 16	13/ 16
	0.25	10/ 13	10/ 13	0/ 0	0/ 0
	0.5	1/ 1	1/ 1	0/ 0	0/ 0
	1	1/ 1	1/ 1	0/ 0	0/ 0
	Total	14/ 17	14/ 17	13/ 16	13/ 16
Haemophilus parainfluenzae	0.12	0/ 0	0/ 0	9/ 10	10/ 10
	0.25	4/ 4	4/ 4	0/ 0	0/ 0
	0.5	1/ 1	1/ 1	0/ 0	0/ 0
	Total	5/ 5	5/ 5	9/ 10	10/ 10
Klebsiella pneumoniae	0.12	0/ 0	0/ 0	7/ 8	7/ 8
	0.5	2/ 2	2/ 2	1/ 1	1/ 1
	1	2/ 2	2/ 2	0/ 0	0/ 0
	Total	4/ 4	4/ 4	8/ 9	8/ 9
Moraxella catarrhalis	0.12	3/ 3	3/ 3	3/ 5	3/ 5
	Total	3/ 3	3/ 3	3/ 5	3/ 5
Staphylococcus aureus (Non-MRSA)	0.12	7/ 9	7/ 9	6/ 6	6/ 6
	0.25	2/ 3	2/ 3	2/ 3	3/ 3
	0.5	0/ 0	0/ 0	0/ 1	0/ 1
	Total	9/ 12	9/ 12	8/ 10	9/ 10
Streptococcus pneumoniae (Non-(PI,PR))	0.03	4/ 4	4/ 4	0/ 0	0/ 0
	0.06	39/ 40	39/ 40	0/ 0	0/ 0
	0.12	1/ 2	1/ 2	0/ 0	0/ 0
	0.5	0/ 0	0/ 0	4/ 4	4/ 4
	1	0/ 0	0/ 0	33/ 38	34/ 38
	2	0/ 0	0/ 0	2/ 2	2/ 2
	Total	44/ 46	44/ 46	39/ 44	40/ 44
Streptococcus pneumoniae (PISP)	0.06	4/ 4	4/ 4	0/ 0	0/ 0
	0.5	0/ 0	0/ 0	1/ 1	1/ 1
	1	0/ 0	0/ 0	5/ 5	5/ 5
	Total	4/ 4	4/ 4	6/ 6	6/ 6
Streptococcus pneumoniae (PRSP)	0.06	2/ 2	2/ 2	0/ 0	0/ 0
	0.12	0/ 1	1/ 1	0/ 0	0/ 0
	0.5	0/ 0	0/ 0	3/ 3	3/ 3
	1	0/ 0	0/ 0	1/ 2	2/ 2
	2	0/ 0	0/ 0	1/ 1	1/ 1
	Total	2/ 3	3/ 3	5/ 6	6/ 6

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Table 39 **Clinical Response at Follow-Up for *S. aureus*, MSSA and MRSA by PVL Status at Baseline (PPB Population: Studies 030A and 030B Combined)**

Baseline Pathogen[1]	SB-275833 n/N	SB-275833 Success Rate (%)	SB-275833 P-Value[1]	Cephalexin n/N	Cephalexin Success Rate (%)	Cephalexin P-Value[1]	Diff in Rates (%)
***S. aureus* (all)**	365/409	89.2		157/173	90.8		-1.5
PVL positive	79/101	78.2	0.0001	34/36	94.4	0.7401	-16.2
PVL negative	285/307	92.8		122/135	90.4		2.5
MSSA	330/358	92.2		133/146	91.1		1.1
PVL positive	64/74	86.5	0.0519	24/24	100	0.2178	-13.5
PVL negative	265/283	93.6		108/120	90.0		3.6
MRSA	35/51	68.6		23/26	88.5		-19.8
PVL positive	15/27	55.6	0.0400	10/12	83.3	0.5800	-27.8
PVL negative	20/24	83.3		13/14	92.9		-9.5

Data Source: Table 7.690

1. P-values are calculated with Fisher's exact tests within each treatment arm and are not adjusted for multiplicity.

Note: not all S. aureus were identified as being PVL+/- nor MRSA/MSSA, and thus it is not always possible to tally within these groups

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- Review of **clinical trial results** (cont.)
  - Correlate MIC results and disk diffusion results (e.g. scattergrams)

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Figure 4-95: Error-rate bounded analysis for discrepancy rates for data from CAP protocols (308 and 313) based on proposed MIC and zone interpretive criteria Tigecycline 50 mg microbiologically evaluable patients *S. pneumoniae* (PSSP): All infections

≤ 0.06 mcg/mL = Susceptible
≥ 19 mm = Susceptible

Plot shows number of isolates at each MIC and zone diameter

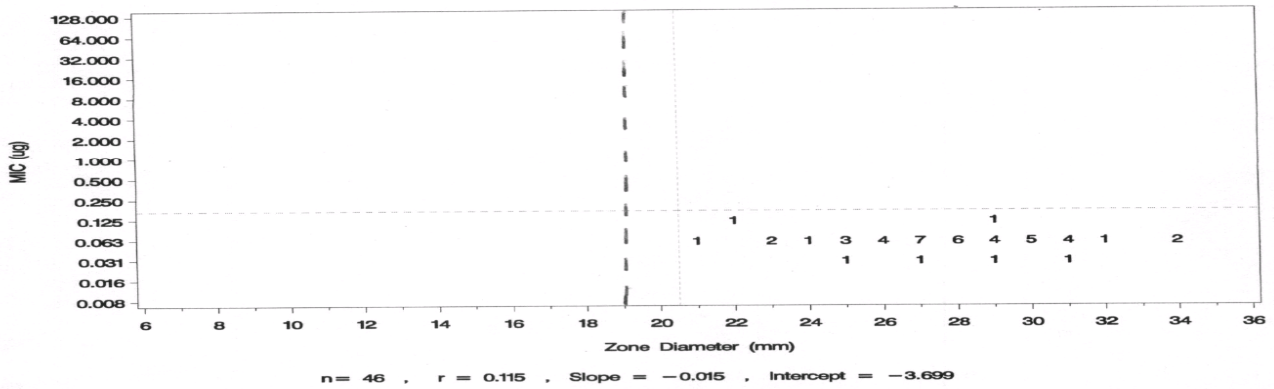

Table 4-30: Discrepancy rates for data from CAP protocols (308 and 313) based on proposed MIC and zone interpretive criteria Tigecycline 50 mg microbiologically evaluable patients *S. pneumoniae* (PSSP): All infections

MIC Range	Number of Isolates	Number of Discrepancies (Discrepancy Rate)		
		Very Major (%)	Major (%)	Minor (%)
≥ (R+1)	0	0	NA	NA
R+S	0	2 (4%)	0	NA
≤ (S-1)	46	NA	0	NA
Total	46	0	0	NA

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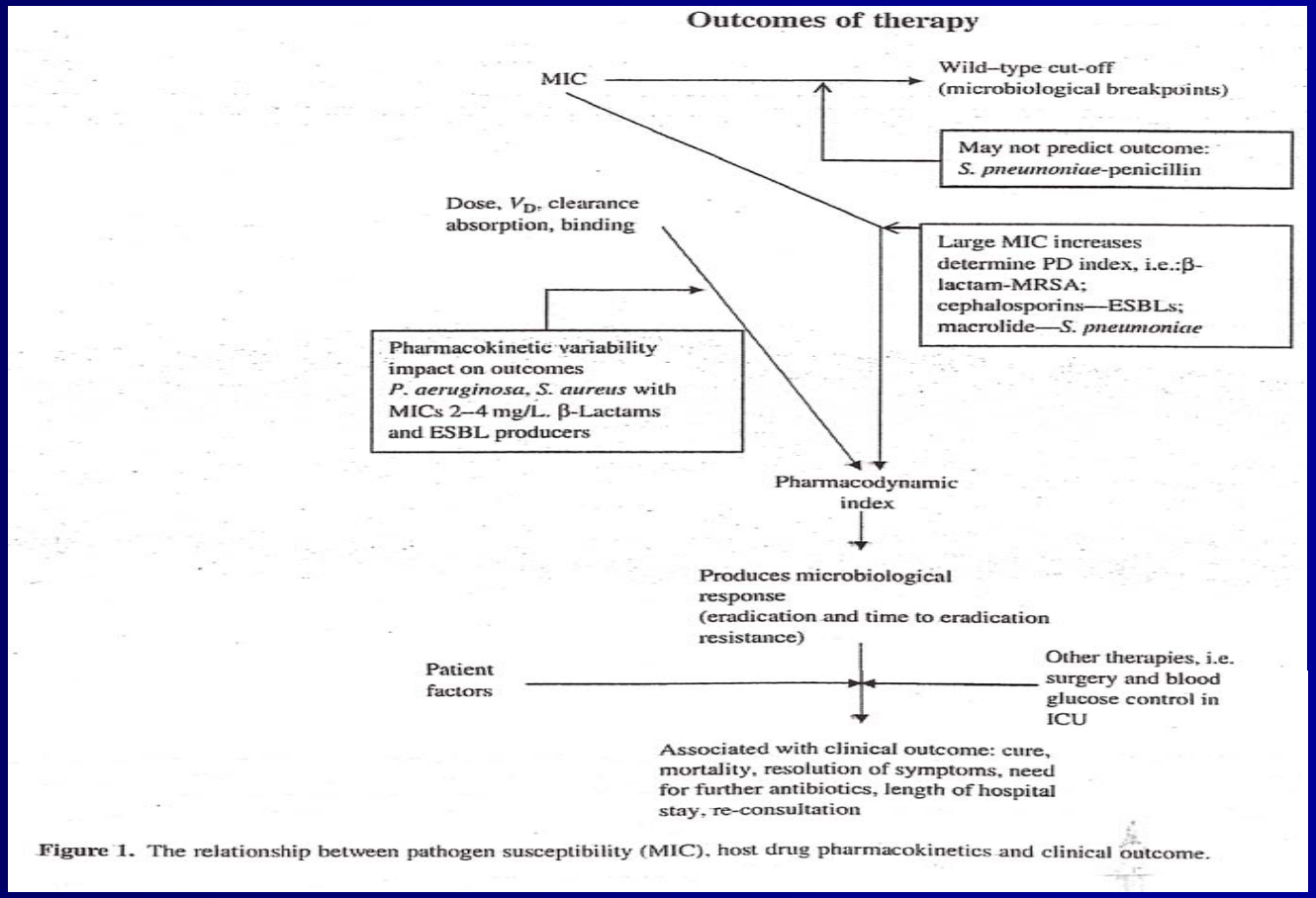

Figure 1. The relationship between pathogen susceptibility (MIC), host drug pharmacokinetics and clinical outcome.

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- Conclusions from review of clinical trial data
  - Appropriate drug for indication and target pathogen
  - Final interpretive criteria based on:
    - surveillance data, animal and human PK/PD, clinical and microbial eradication, clinical experience at particular MICs
  - Final susceptibility test quality control parameters
  - Limitations of susceptibility test methods (e.g. microbroth dilution versus agar dilution)

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- Microbiology Subsection of Package Insert
  - Process
    - Standard wording in FDA labels
    - Wording to be determined (e.g. mechanism of action)
    - Interpretive criteria
    - QC criteria
  - Correlation with other sections of label (e.g. pharmacology, Indications and Usage)
  - Final interpretive criteria based on:
    - surveillance data, PK/PD, clinical and microbial eradication, **clinical experience at particular MICs**

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Table 3-30: Clinical and Microbiologic Response by MIC Value for Selected Baseline Isolates: Microbiologic Modified Intent-to-Treat Population in Studies 308 and 313 (Cont'd)

		---Tigecycline 50 mg---		---Levofloxacin---	
Pathogen	MIC (μg/ml)	Clinical Response Cure n / N	Microbiologic Response Eradication n / N	Clinical Response Cure n / N	Microbiological Response Eradication n / N
Streptococcus pneumoniae (Non-(PI,PR))	0.03	4/ 7	5/ 7	0/ 0	0/ 0
	0.06	40/ 43	41/ 43	0/ 0	0/ 0
	0.12	1/ 3	1/ 3	0/ 0	0/ 0
	0.5	0/ 0	0/ 0	4/ 5	4/ 5
	1	0/ 0	0/ 0	36/ 44	37/ 44
	2	0/ 0	0/ 0	2/ 2	2/ 2
	Total	45/ 53	47/ 53	42/ 51	43/ 51
Streptococcus pneumoniae (PISP)	0.06	4/ 5	4/ 5	0/ 0	0/ 0
	0.5	0/ 0	0/ 0	1/ 1	1/ 1
	1	0/ 0	0/ 0	5/ 5	5/ 5
	Total	4/ 5	4/ 5	6/ 6	6/ 6
Streptococcus pneumoniae (PRSP)	0.06	3/ 3	3/ 3	0/ 0	0/ 0
	0.12	0/ 1	1/ 1	0/ 0	0/ 0
	0.5	0/ 0	0/ 0	3/ 3	3/ 3
	1	0/ 0	0/ 0	1/ 2	2/ 2
	2	0/ 0	0/ 0	1/ 1	1/ 1
	Total	3/ 4	4/ 4	5/ 6	6/ 6

Abbreviations: MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; PI = penicillin intermediate; PR = penicillin resistant; PISP = penicillin intermediate *S. pneumoniae*; PRSP = penicillin resistant *S. pneumoniae*.
Source: MMMICC1 - 23JUN06 09:15

The clinical and microbiologic response by MIC value for all baseline isolates in the studies for the ME and m-mITT populations are summarized in 5.3.5.3, Efficacy Supportive Tables, CAP, ST 3-15 and ST 3-16, respectively.

The MIC values, clinical responses, and microbiologic responses of the selected baseline isolates excluding contaminants are summarized separately for those ME subjects with monomicrobial infections in Table 3-31 and those in polymicrobial infections in Table 3-32.

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WHAT CLINICAL MICROBIOLOGY INFORMATION IS NEEDED TO UPDATE OUTDATED CLINICAL MICROBIOLGY INFORMATION IN FDA LABELS?

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- Reasons for Breakpoints to Become Outdated
  - Shift in susceptibility of wild type population
  - New PK/PD information
  - New mechanisms of resistance
  - Modified susceptibility test methods
  - New susceptibility test media
  - Change in Quality Control Parameters

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- No FDA clinical microbiology laboratory capacity to address

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- Information needed for setting interpretive criteria (breakpoints)
  - In vitro microbiological data
  - In vitro resistance markers (phenotypic and genotypic)
  - Animal and human PK/PD data
  - Clinical and microbiological outcome from prospective clinical trials
- No single set of information provides all necessary information

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- So What Is Needed to Redefine Interpretive Criteria and Quality Control Parameters
  - In vitro susceptibility data generated by up to date, scientifically sound standardized susceptibility test methods accepted by the scientific and medical communities
    - being done
  - Current in vitro susceptibility data on microorganisms
    - active surveillance programs to obtain data
      - being done
  - On going surveillance for new mechanisms of antimicrobial resistance
    - being done

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- So What Is Needed (cont.)
  - On going evaluation of what shifts in antimicrobial susceptibility patterns and new mechanisms of resistance mean to the interpretation of susceptibility tests and the efficacy of the antimicrobial
    - being done
  - Reevaluation of the PK/PD parameters of drugs by current methods and technologies
    - being done

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- So What Is Needed (cont.)
  - Surveillance of the literature to detect changes in the efficacy of antimicrobial treatments
    - being done
      - individual case reports
        - however, reports may be sporadic, and often incomplete,

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- So What Is Needed (cont.)
- Reviews of individual case reports
  - Compilation of individual reports and thus suffers from some deficiencies as sum of individual report
- Non-FDA clinical studies
  - Majority do not meet criteria of adequate and well controlled, usually not adequately powered

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- So What Is Needed (cont.)
- Biggest part of puzzle
  - Clinical and microbiological outcome from prospective adequate and well controlled clinical trials
    - Ideal along with other components
      - Possible but for older antimicrobials not probable

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- What is ACCEPTABLE to redefine interpretive criteria and quality control parameters?
  - Current surveillance data for pathogens against older antimicrobials?
  - Current PK/PD information for older antimicrobials?
  - None or minimal clinical efficacy data?

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- What is ACCEPTABLE (cont.)
  - Is it necessary to have complete data or is "sufficient data" from standards organization okay?
    - "Sufficient data"
      - Incomplete notes on discussions behind changes that occurred but it is recognized that the issue was discussed among experts in the field and a majority vote okayed the changes and changes reflect current scientific and medical thinking.
      - Minimal clinical studies but studies are determined to be adequate

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- What happens in the event of a discrepancy between up to date FDA information in PI and standard organization information
  - Discussions between drug company, FDA and standards organization

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- Implementation of changes
  - Process defined by regulation
    - Change in label must first be done by reference listed drug (RLD) company before it can be done by generic company

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- Slide Acknowledgements
  - Slides 7, 8, 17
    - Turnidge J and DL Paterson. 2007. Clinical Microbiology Reviews. 20:391-408
  - Slide 12
    - Frimodt-Moller N. 2002. International Journal of Antimicrobial Agents. 19:333-339.
  - Slide 19
    - Ambrose PG. 2006. Pharmacotherapy 26:129-134
  - Slide 34
    - MacGowan AP. 2008. Journal of Antimicrobial Chemotherapy 62 Suppl 2:ii105-ii114.